REMARKS

Applicants respectfully request entry of amendments to claims 10 and 22 and cancellation of claim 38 without prejudice or disclaimer. Support for the amendments can be found throughout the specification and the originally filed claims and, therefore, do not add new matter.

Applicants submit that pending claims 1, 10, 13, 15, 16, 22, 23, 25-29, 32, and 35-37 are in condition for allowance and respectfully request that the claims as amended be entered.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1, 10, 13, 15, 16, 22, 23, 25-39, 32 and 35-37 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants note that while claims 1, 10, 13, 15, 16, 22, 23, 25-39, 32 and 35-37 are listed as being indefinite, the only claim mentioned is claim 22. Therefore, the response below is directed to claim 22.

The Office Action alleges that the phrase "reduced-serum media" in claim 22 is not defined in the specification. While Applicants do not acquiesce to the reasoning offered in the Action, in order to expedite prosecution toward allowance, the claim has been amended to recite "media containing less than 15% serum." Support for the amendment can be found in the specification as filed. For example, Example 3 details the use of culture media containing less then 15% serum, EGM2mv (Clonetics). In light of the amendment, withdrawal of the rejection of claims under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 1, 10, 13, 15 and 16 under 35 U.S.C. §103(a) as allegedly being unpatentable over Hogan (U.S. Pat. No. 5,453,357; hereinafter, "Hogan" or "the Hogan patent") in view of Shamblott, et al. (1998, PNAS, pp 13726-31, hereinafter, "Shamblott").

The recent U.S. Supreme Court decision in the *KSR International v. Teleflex, Inc.* (127 S.Ct. 1727, 82 USPQ 2d. 1385 (2007)), modified the standard for establishing a *prima facie* case of obviousness. Under the *KSR* rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to

be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references. Applicants respectfully submit that the criteria for establishing a *prima facie* case of obviousness have not been satisfied.

The claims recite a human embryoid body derived (EBD) cell characterized by forming disaggregated single cells upon dissociation from embryoid bodies (EB) and adhering to defined extracellular matrix components lacking a feeder layer and lacking leukemia inhibitory factor; and having the ability to be maintained in culture on the defined extracellular matrix components in the absence of a feeder layer for at least thirty population doublings without being immortal under such conditions. Applicants submit that because the cited references do not teach all the claim limitations, one of skill in the art would not be motivated to combine the reference teachings.

The Office Action alleges, in part, that "Hogan teaches mouse embryoid body cells isolated from mouse embryoid bodies (EB's), rounded colonies of densely packed ES-like cells, produced by the culture of mouse primordial germ cells" and "Shamblott teaches embryoid bodies (EB's) produced from human primordial germ cells (hPGC's)." (Office Action, page 3-4.) The Office Action also alleges that "the ordinary artisan at the time of filing would have reasonably expected the physiological characteristics to be the same for the claimed cells and those of Hogan even given species differences. Thus, the cells of Hogan in view of Shamblott undergo at least 30 or at least 60 population doublings, proliferate under conditions nonpermissive for the proliferation of human EG cells, proliferate under culture conditions lacking LIF, a fibroblast feeder layer, or both, and transfectable with a retrovirus, lentivirus or both. There is no evidence to the contrary on the record." (Office Action, page 4.)

Applicants respectfully submit that the Examiner has mischaracterized the teachings of the Hogan. In contrast to the Examiner's assertion that "Hogan teachees mouse embryoid body cells...." and Hogan teaches "picking of single clones of EB-derived mouse cells..." (page 3 of Office Action), Hogan does not provide any EB-derived cells at all. Hogan describes in column 6, lines 19-50, not EB-derived cells, but rather cells that are derived from embryos and are

referred to as primordial Germ Cells (GCs). GCs, in contrast to Applicant's EB-derived cells, require a feeder layer for growth. Hogan's GC cells, in contrast to Applicant's EB-derived cells can give rise to embryoid bodies but they are not DERIVED from embryoid bodies. Such GC cells of Hogan are pluripotential cells that under certain conditions, can differentiate INTO embryoid bodies, from which Applicant's cells can then be derived. However, Hogan does not teach cells derived from the embryoid bodies at all. Further, for the sake of argument, even if Hogan had described cells further derived from the mouse embryoid bodies, it would not provide the human cells of the invention. Mouse EBD cells have very limited capacity for proliferation in culture if they are not immortalized. In sharp contrast, Applicant's human EBD cells are capable of long periods of cell proliferation and passages for years.

Similarly, Shamblott describes the derivation of pluripotent stem cells from germ cells, not from embryoid bodies. The mouse *germ cells* of Hogan and the human *germ cells* of Shamblott were cultured in the presence of a fibroblast feeder layer and leukemia inhibitory factor (LIF). All of the cells described in Hogan and Shamblott would not proliferate in the absence of a fibroblast feeder layer, LIF, or both. The combination of the germ cells taught in Hogan and the germ cells taught in Shamblott, both of which require feeder layers for growth, cannot render a human cell derived from an embryoid body that does not require LIF or a feeder layer for proliferation, obvious in any way. The human primordial germ cells of Shamblott were grown for 20-25 doublings on a fiberblast feeder layer, but again, these are germ cells and not embryoid body derived cells. Shamblottt mentions production of EBs from the PGCs but there is no suggestion that such cells should be cultured in the absence of feeder layers and/or LIF.

Since Hogan is silent as to obtaining cells from a mouse or human embryoid body, let alone cells that do not grown on a feeder layer and LIF, and Shamblott similarly teaches germ cells that require a feeder layer and LIF, one of skill in the art would have no motivation to combine the references to arrive at Applicant's invention and even if they did, they would not end up with embryoid body derived cells. Thus, the combination of Hogan and Shamblott cannot render obvious the claims of the application, in which the EBD cells are maintained in

culture in the absence of a feeder layer and lacking leukemia inhibitory factor for at least thirty population doublings without being immortal.

Applicants submit that because there is no reasonable expectation of successfully achieving the invention as claimed, no *prima facie* case for obviousness exists. Further, there is no teaching or suggestion of all of the recited claim limitations. Accordingly, withdrawal of rejection of claims 1, 10, 13, 15 and 16 under 35 U.S.C. §103 is respectfully requested.

Applicant respectfully traverses the rejection of claims 22, 25-29, 32, 35, 36 and 38 under 35 U.S.C. §103(a) as allegedly being unpatentable over Hogan in view of Shamblott. Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness.

The Office Action alleges that "Hogan teaches a method of producing EBD-cells comprising culturing primordial germ cells to form an embryoid body, rounded colonies of densely packed ES-like cells, digesting the embryoid body with trypsin to provide EBD-cells and culturing the EBD-cells in media comprising hFGF2" and "PGC culture media contains 15% FBS." (Office Action, pages 6-7.) The Office Action also alleges that "Shamblott teaches embryoid bodies (EB's) produced from human primordial germ cells (hPCG's)" and that "it would have been obvious to the ordinary artisan to follow the method of Hogan to produce human EBD cells given the method of producing human EB's from hPGC culture as taught by Shamblott." (Office Action, pages 7-8.) Additionally, the Office Action indicates that "Applicant ought to consider amending the claims to insert active method steps that distinguish the method claims from those of the prior art. This may overcome the art rejection over the method claims." (Office Action, page 8.)

As stated above, neither Hogan nor Shamblott teach or describe an embryoid derived cell at all. Hogan's GC cells, in contrast to Applicant's EB-derived cells can give rise to embryoid bodies but they are not DERIVED from embryoid bodies. Such GC cells of Hogan are pluripotential cells that under certain conditions, can differentiate INTO embryoid bodies, from which Applicant's cells can then be derived. However, Hogan does not teach cells derived from the embryoid bodies at all. Further, for the sake of argument, even if Hogan had described

cells further derived from the mouse embryoid bodies, it would not provide the human cells of the invention. Mouse EBD cells have very limited capacity for proliferation in culture if they are not immortalized. In sharp contrast, Applicant's human EBD cells are capable of long periods of cell proliferation and passages for years.

Similarly, Shamblott describes the derivation of pluripotent stem cells from germ cells, not from embryoid bodies. The mouse *germ cells* of Hogan were cultured on a fibroblast feeder layer and LIF and the human *germ cells* of Shamblott were cultured in the presence of a fibroblast feeder layer. The cells described in Hogan and Shamblott would not proliferate in the absence of a fibroblast feeder layer, LIF, or both. The combination of the germ cells taught in Hogan and the germ cells taught in Shamblott, both of which require feeder layers for growth, cannot render a human cell derived from an embryoid body that does not require LIF or a feeder layer for proliferation, obvious in any way. The human primordial germ cells of Shamblott were grown for 20-25 doublings on a fibroblast feeder layer, but again, these are germ cells and not even embryoid body derived cells.

Applicants have amended the claims herein to insert active method steps, in particular, culturing the cells without LIF in the absence of a feeder layer. As such, the teachings of Hogan would not result in the claimed method of obtaining a human embryoid body derived (EBD) cell comprising: (a) culturing primordial germ cells in a media comprising human basic fibroblast growth factor and lacking leukemia inhibitory factor under conditions that are suitable for formation of a solid or cystic embryoid body having a 3-dimensional morphology; (b) disaggregating the solid or cystic embryoid body under suitable enzymatic conditions to provide a constituent cell or embryoid body derived (EBD) cell; and (c) culturing the EBD cell in the absence of a feeder layer wherein the cell is characterized as forming disaggregated single cells upon dissociation from embryoid bodies (EB) for at least 30 population doublings without being immortal under these conditions; and wherein the media is selected from the group consisting of serum-free media and media containing less than 15% serum. As such, the combination of

Hogan and Shamblott would not allow one of skill in the art to perform the claimed method and in fact would not provide any teaching past step (a) of the claimed invention.

Thus, the combination of Hogan and Shamblott cannot render obvious the claims of the application, in which a method of obtaining EBD cells in media lacking leukemia inhibitory factor, and culturing the cells in the absence of a feeder layer for at least thirty population doublings without the cells becoming immortal.

Applicants submit that because there is no reasonable expectation of successfully achieving the invention as claimed, and there is no motivation to combine the cited references, no *prima facie* case for obviousness exists. For these reasons, Applicants respectfully request that the rejection, including as it might be applied against the amended claims, be withdrawn.

Applicants respectfully traverse the rejection of claims 22, 27-29, 36 and 37 under 35 U.S.C. §103(a) as allegedly being unpatentable over Hogan in view of Shamblott, further in view of Rohwedel et al (1996, Cel Biol. Internat. 20, pp 579-87, hereinafter, "Rohwedel"). Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness.

The Office Action alleges, in part, that "Rohwedel teaches the culture and expansion of mouse ES cells on tissue culture plates coated with gelatin for morphological studies" and that it would be "obvious to follow the method of Hogan to produce human EBD cells given the method of producing human EB's from hPGC culture as taught by Shamblott, culturing the EBD cells on collagen I coated plates." (Office Action, pages 9-10.)

The arguments against the combination of Hogan and Shamblott stated above apply equally and are incorporated here. Applicants submit that the addition of Rohwedel does not cure the deficiencies in Hogan and Shamblott. Rohwedel cultivates cells on plates coated with gelatin in order to differentiate them into cardiac, skeletal muscle, and neuronal cells. Thus, the combination of Hogan, Shamblott and Rohwedel cannot render obvious the claims of the invention which require the the cells are capable of growth of the EBD cells in media lacking leukemia inhibitory factor and a feeder layer for at least thirty population doublings without the cells becoming immortal.

Applicants submit that because there is no reasonable expectation of successfully achieving the invention as claimed, and there is no motivation to combine the cited references, no *prima facie* case for obviousness exists. For these reasons, Applicants respectfully request that the rejection, including as it might be applied against the amended claims, be withdrawn.

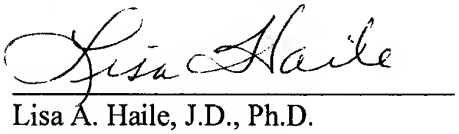
CONCLUSION

Applicants submit that pending claims 1, 10, 13, 15, 16, 22, 23, 25-29, 32, and 35-37 are in condition for allowance. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this submission.

The Commissioner is hereby authorized to charge $245.00 as payment for the Petition for Two-Month Extension of Time fee to Deposit Account No. 07-1896. No other fees are believed to be due with the filing of this paper. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

Date: January 6, 2009



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